

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cohort profile: The multi-site prospective Liver Disease and Reproductive Aging (LIVRA) study in U.S. women living with and without HIV
AUTHORS	Price, Jennifer; Ma, Yifei; Adimora, Adaora; Fischl, Margaret; French, Audrey L.; Golub, Elizabeth; Konkle-Parker, Deborah; Kuniholm, Mark H.; Ofotokun, Ighovwerha; Plankey, PhD, Michael; Sharma, Anjali; Tien, Phyllis

VERSION 1 – REVIEW

REVIEWER	Pokorska-Śpiwak, Maria Medical University of Warsaw
REVIEW RETURNED	27-Aug-2021

GENERAL COMMENTS	<p>In this paper the authors to evaluate the contributions of HIV, HCV, and reproductive aging to steatosis and fibrosis progression as measured by longitudinal vibration controlled transient elastography (VCTE) among a large cohort of women living with or without HIV. The cohort is well described as well as methods used. I have only minor comments that might be explained to bring a clearer message:</p> <ol style="list-style-type: none">1. Line 24: Why was HCV RNA testing performed at least 2 years after detection of anti-HCV and not earlier?2. What proportion of participants with chronic hepatitis C underwent treatment? What was the reason for treatment delay in the remaining group?3. According to the presented data, 89% of HIV-infected women received ART. As several ARV drugs may lead to hepatotoxicity, it would be reasonable to include the information on the ART regimens used and their influence on the liver fibrosis and steatosis.4. Liver steatosis occurred less frequently in participants with HCV infection. As hepatitis C is considered as one of the possible causes of liver steatosis, it is an interesting finding, please discuss.5. Finding that the factors associated with steatosis and fibrosis were similar after excluding VCTE examinations with IQR/median >30%, success rate <60%, poor image quality, or any of these three criteria is indeed interesting. However, due to general recommendations, these results should not be considered valid and therefore should not be accepted in the clinical practice. Please discuss.
-------------------------	---

REVIEWER	Pagano, Stefano University of Perugia, Department of Surgical and Biomedical Sciences, Unit of Paediatric Dentistry Dental materials epidemiology
REVIEW RETURNED	23-Dec-2021

GENERAL COMMENTS	<p>This is a very well done study of LIVRA in women in the US with and without HIV</p> <p>I congratulate the authors for the high number of the sample and for conducting the study.</p> <p>Just two observations:</p> <ul style="list-style-type: none"> -Check that the keywords are Pubmed MESH terms -The introduction section is the one that presents the greatest criticalities. It needs to be reorganized in a more orderly way -Line 20, however, the general indications on recruitment, even if briefly, must be reported in the text -The approval of the bioethical committee of references for the enrollment of patients is lacking
-------------------------	---

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Maria Pokorska-Śpiewak, Medical University of Warsaw Comments to the Author:

In this paper the authors to evaluate the contributions of HIV, HCV, and reproductive aging to steatosis and fibrosis progression as measured by longitudinal vibration controlled transient elastography (VCTE) among a large cohort of women living with or without HIV. The cohort is well described as well as methods used. I have only minor comments that might be explained to bring a clearer message:

1. Line 24: Why was HCV RNA testing performed at least 2 years after detection of anti-HCV and not earlier?

At study entry, HCV RNA was tested in all women who were anti-HCV positive. Retrospective anti-HCV testing identified women who seroconverted to anti-HCV positive. In these cases, we performed HCV RNA at least 2 years after seroconversion to allow time to determine whether they had spontaneously cleared the infection.

2. What proportion of participants with chronic hepatitis C underwent treatment? What was the reason for treatment delay in the remaining group?

Among the anti-HCV positive women, 30% cleared HCV with treatment, 28% cleared HCV spontaneously, and 42% remained viremic at the baseline LIVRA visit. This information was added to the main text of the manuscript. Ongoing HCV viremia may have been due in part to timing of the baseline LIVRA visit, as the cohort started enrolling prior to the availability of direct acting antivirals (DAAs) or in the early DAA period when access was more restricted. An analysis within the WIHS found that women with annual income \leq \$18,000 and women who injected drugs were less likely to initiate HCV treatment from 2015-2018, whereas women living with HIV and women who were employed were more likely to initiate treatment (PMID: 33141170).

3. According to the presented data, 89% of HIV-infected women received ART. As several ARV drugs may lead to hepatotoxicity, it would be reasonable to include the information on the ART regimens used and their influence on the liver fibrosis and steatosis.

Thank you for this comment. We have added type of ART regimen to Table 2. We have also added to the “findings to date” section the lack of association of ART (or other HIV-related variables) with CAP or LS in the analysis limited to women living with HIV. The potential influence of ART regimen on incident fibrosis and steatosis is an area of high interest and will be evaluated prospectively in the cohort.

4. Liver steatosis occurred less frequently in participants with HCV infection. As hepatitis C is considered as one of the possible causes of liver steatosis, it is an interesting finding, please discuss.

We agree that this is a highly interesting finding and is consistent with our prior study among men and women with and without HIV and HCV who underwent magnetic resonance spectroscopy (PMID: 27981599). Due to space restrictions, we were unable to include a full analysis and discussion of this finding in our cohort description, but we have added a reference to our prior publication.

5. Finding that the factors associated with steatosis and fibrosis were similar after excluding VCTE examinations with IQR/median >30%, success rate <60%, poor image quality, or any of these three criteria is indeed interesting. However, due to general recommendations, these results should not be considered valid and therefore should not be accepted in the clinical practice. Please discuss.

We added more context by stating that in the setting of a large multicenter epidemiologic study, these findings provide assurance about the rigor of our data collection approach. However, in clinical practice, currently accepted VCTE validity criteria should be adhered to.

Reviewer: 2

Dr. Stefano Pagano, University of Perugia Comments to the Author:

This is a very well done study of LIVRA in women in the US with and without HIV I congratulate the authors for the high number of the sample and for conducting the study.

Just two observations:

-Check that the keywords are Pubmed MESH terms

Thank you- we have revised the keywords to ensure that they are Pubmed MESH terms.

-The introduction section is the one that presents the greatest criticalities. It needs to be reorganized in a more orderly way

Thank you for this suggestion- we have reorganized the introduction section for clarity.

-Line 20, however, the general indications on recruitment, even if briefly, must be reported in the text

We have added more information regarding recruitment to the “study population and design” section.

-The approval of the bioethical committee of references for the enrollment of patients is lacking

We have added additional details regarding the Institutional Review Boards to the end of the “Study Population and Design” subsection in the “COHORT DESCRIPTION” section.